Attorney Docket No.: P-7216-US3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	SHOENFELD, Yehuda	Examiner:	NAVARRO, Albert Mark
Serial No.:	09/405,050		
Filed:	September 27, 1999		
Title:	IMMUNOTHERAPEUTIC METHOD OF TREATING CANCEROUS DISEASES BY ADMINISTRATION OF GAMMA GLOBULINS		

REMARKS

Sir:

The present response is intended to be fully responsive to all points of rejection raised by the Examiner in the Office Action dated April 29, 2005 and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Applicants assert that the present invention is new, non-obvious and useful. Prompt consideration and allowance of the claims is respectfully requested.

Status of Claims

Claims 1-11 and 22-29 are pending in the application. Claims 1-11 and 22-29 have been rejected.

Double Patenting Rejections

In the Office Action, the Examiner rejected claims 1-11 and 22-29 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims U.S. Patent No. 5,965,130.

Applicants hereby offer to provide a terminal disclaimer upon indication by the Examiner of allowable claims.

In the Office Action, the Examiner rejected claims 1-10 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims U.S. Patent No. 5,562,902.

Applicants hereby offer to provide a terminal disclaimer upon indication by the Examiner of allowable claims.

CLAIM REJECTIONS

35 U.S.C. § 112 Rejections

In the Office Action, the Examiner rejected claims 1-11 and 22-29 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed Invention, a new matter rejection is maintained.

Specifically, the Examiner alleges that recitation in the claims, that the inhibition must take place in a mammal which has "metastatic lymphoma," has no guidance in the specification to isolate a subgenus of individuals who have active metastatsis from those who do not - for treatment, or any mention pertaining specifically to lymphomas, as recited in the instantly filed claims. In essence, the Examiner alleges that a distinction between a population with "active" metastasis and "passive" metastasis must be taught in the subject application.

Applicants respectfully disagree. Applicants assert that is well established in the art, that there is no distinction between subpopulations with "active" or "passive" metastasis. Once metastasis has occurred, it is by its nature active. There is no subgenus of "passive" metastasis and once a malignant tumor develops, it is either metastatic or focal. Applicants maintain that the instant invention as claimed, adequately teaches treatment of the metastasis as a whole. As applicants asserted before, and the Examiner confirmed, one of the phenotypic differences between primary tumor cells and metastatic cells is the upregulation of MMP's, necessary for active invasion of basal membranes, making the metastatic cells active.

In view of the above, Applicants submit that sufficient support exists for claims directed to inhibiting or treating metastastatic lymphoma in a mammal which comprises administering to the mammal a preparation of IVIG. Accordingly, Applicants request withdrawal of the 112 rejection.

In the Office Action, the Examiner alleges that the phenotypical distinction between metastatic and primary tumor cells is several fold more pronounced with different types of cancers, such as lymphomas, to which the claims are directed versus carcinomas and sarcomas as set forth in the Examples 1-5, negates Applicants' assertion that support for the treatment of metastatic lymphoma is supported Examples 1-5. Applicants respectfully disagree.

The assertion that support for the use of a preparation of IVIG for treating metastastatic lymphoma in a mammal does not rest solely on Examples 1-5, but also on Example 8, which clearly demonstrated that lymphoma cells are responsive to Intravenous Immunoglobulins (IVIG) (Page 19, lines 1-2), inhibiting cell proliferation.

As demonstrated in Example 1, IVIG was effective in inhibiting metastatic melanoma *in-vivo* (page 7, lines 27-29, noting that a single treatment reduced metastatic foci by 81%) and in Example 2, metastatic sarcoma *in-vivo* as well (page 13, line 13, noting few small tumors in animals treated with intact IVIG). Similarly, T-cell lymphoma cells became apoptotic when exposed to IVIG in a dose dependent manner, when the concentration of IVIG was similar to that found in the blood of patients treated with IVIG (page 18, line 28, to page 19 line 2). Therefore, a person of ordinary skill in the art would recognize that treatment with a preparation of IVIG will likewise be effective in treating metastatic lymphoma in a patient.

In addition, as a person skilled in the art would recognize, several metastatic cells' biomarkers exist, that are the same across various cancer origins such as melanoma, sarcoma and lymphoma.

An example of these markers are described in Aoudjit et al., (Fawzi Aoudjit, Edouard F. Potworowski, and Yves St-Pierre. (1998) *The Metastatic Characteristics of Murine Lymphoma Cell Lines In Vivo Are Manifested After Target Organ Invasion* Blood, Vol. 91 No. 2: pp. 623-629 noted that LFA-1 (a cell adhesion molecule (CAMs)), has been strongly correlated with the metastatic potential of several tumor cells such as hepatomas, melanomas, mammary carcinomas, and lymphomas. Treatment with anti-LFA-1, -CD44 and -$\alpha 5\beta 3$ MoAbs was shown to block lymphoma metastasis. These observations establish a link between the metastatic potential of tumor cells and their ability to home to target organs.

Similarly, Sun Sy et al, (Man Sun Sy, yaoJun Guo, and Ivan Stamenkovic (1991) *Distinct Effects of Two CD44 Isoforms on Tumor Growth In Vivo*. J Exp Med. Oct 1;174(4):859-66 asserted that invasiveness of human bladder carcinoma cells has been shown to correlate with the level of expression of CD44, as well as high expression of CD44 was demonstrated to be associated with aggressive behavior and poor prognosis of human non-Hodgkin's lymphomas.

In yet another example, Geradts et al., (Joseph Geradts, Robert Maynard, Michael J. Birrer, Denver Hendricks, Susan L. Abbondanzo, Kwun M. Fong, J. Carl Barrett and Donald P. Lombardi (1999). *Frequent Loss of KAI1 Expression in Squamous and Lymphoid Neoplasms*, An Immunohistochemical Study of Archival Tissues American Journal of Pathology;154:1665-1671), in testing levels of KAI1 in lymphoma metastases, noted that *KAI1* is down-regulated in several common types of human malignancies, including carcinomas of the prostate, lung, breast, bladder, and colon, and this down-regulation is associated with more aggressive behavior, such as metastasis.

It would therefore be clear to a person skilled in the art, at the time of filing, that since there are common biomarkers among several cancer types, there could be a common treatment that would be effective in treating metastatic cancer of several types.

Applicants therefore maintain that sufficient support exists for claims directed to inhibiting or treating metastastatic lymphoma in a mammal which comprises administering to the mammal a preparation of IVIG. Accordingly, Applicants request withdrawal of the 112 rejection.

In the Office Action, the Examiner alleges that it is the selection of a species of only those who have metastatic lymphoma, in the claims, rather than, as Applicants assert; that as set forth in MPEP 2164.02, sufficient support for a claimed genus (treatment of cancer metastasis with IVIG) exists, since the specification contains representative examples together with a statement applicable to the genus as a whole (Page 1, lines 2-4 and page 3, lines 15-17 and 19), which is deemed to be new matter.

Applicants respectfully disagree. Applicants assert, that since the genus of treatment of cancer metastasis with IVIG is enabled in view of MPEP 2163 (II)(A)(3)(a), and in view of the level of skill and knowledge in the art (high education levels of oncology MDs), the partial structure disclosed (Fab fragments, Example 3), the chemical properties, the functional characteristics coupled with disclosed correlation between structure and function, as shown in Examples 1-8 and the detailed disclosure of the method of making the claimed invention (see e.g. page 8, line 29, to page 10, line 2) which were well known in the art at the time of filing, make the claiming of any combination of such identifying characteristics that distinguish the claimed invention from other materials, in this case, the treatment of metastatic lymphoma using IVIG, appropriate.

In view of the above, Applicants submit that sufficient support exists for claims directed to inhibiting or treating metastastatic lymphoma in a mammal which comprises administering to the mammal a preparation of IVIG. Accordingly, Applicants request withdrawal of the 112 rejection.

As Applicants noted before, the specification does gives considerable direction and guidance (Examples 1-5 and 8), a high level of skill in the art existed at the time the application was filed and all of the methods needed to practice the invention were well known and in addition, working examples exist in the specifications (see e.g. *In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1403-07). Therefore, a person of ordinary skill in the art would recognize that IVIG preparation would be effective in treating metastatic lymphoma, as recited herein, without undue experimentation.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

Mark S. Cohen
Attorney/Agent for Applicant(s)
Registration No. 42,425

Dated: April 26, 2006

Pearl Cohen Zedek Latzer, LLP
1500 Broadway
12th Floor
New York, New York 10036
Tel: (646) 878-0800
Fax: (646) 878-0801